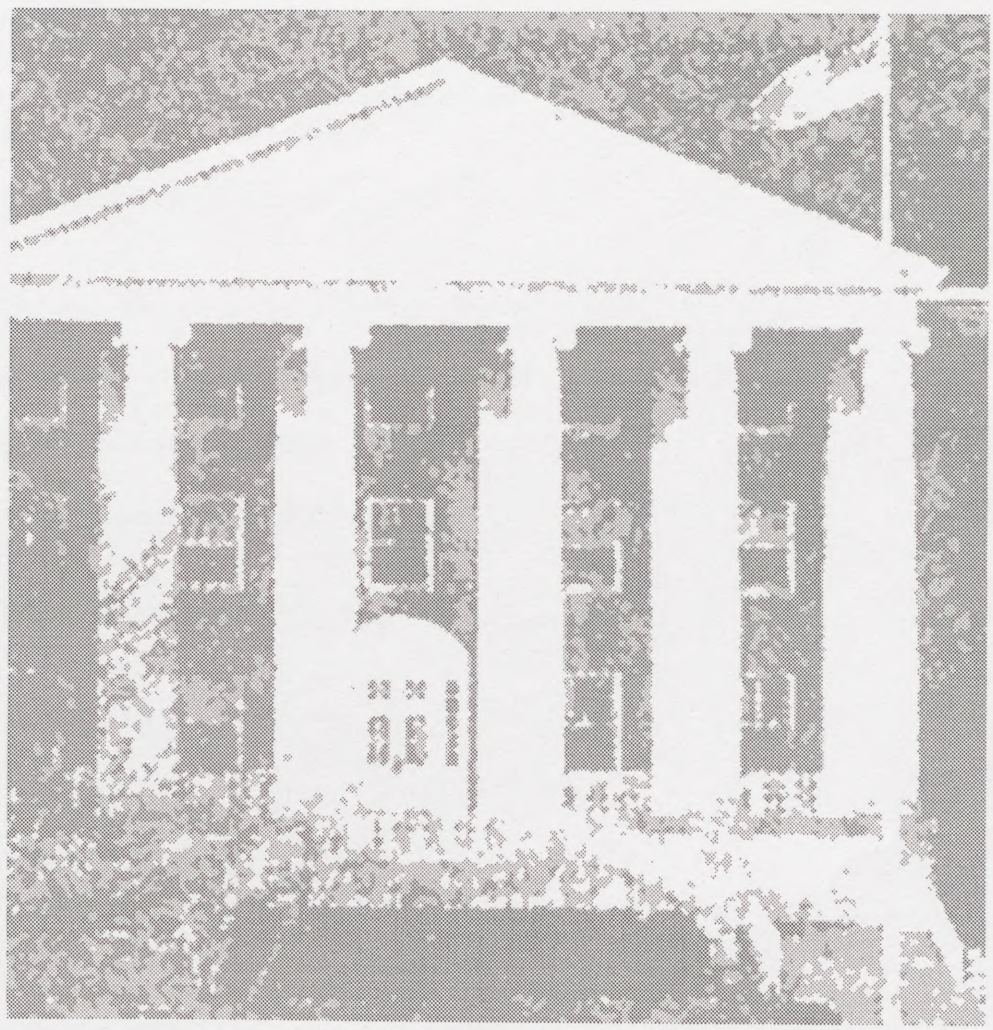
Setting Research Priorities

at the National Institutes of Health



NATIONAL INSTITUTES OF HEALTH

SETTING RESEARCH PRIORITIES
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OVERVIEW

Given the importance of medical research in fighting disease and improving the nation's health, the enormous range of possible subjects of research, and the thousands of talented investigators who seek funding, the National Institutes of Health (NIH) must make choices about where and how it spends its money, approximately $13 billion in fiscal year 1997.

The process of choosing is routinely called setting priorities, a phrase that is shorthand for an elaborate application of principles and mechanisms the NIH uses for evaluation and judgment. Making choices is complex and often difficult: the NIH's mission and its history demonstrate that no one thing–no single disease, no single investigator, no single Institute, no single method of funding research–comes first or claims permanent priority over others. The principles and mechanisms that guide the NIH in the continuous activity of managing its budget are the subject of this booklet. Some observations about the influences and facts that condition the process may add clarity. It is important, however, to keep in mind that this booklet describes the ways things work at the NIH now; it is neither a justification nor a defense of a system that has succeeded, but which also is imperfect.

Managing the NIH's budget requires many decisions.

There are 21 Institutes and Centers (called Institutes for convenience) within the NIH. By law each must be funded and each is committed to certain domains of medical science (e.g., cancer, heart disease, aging, mental health). Their existence sets rough limits on both the current budget and future budgets.

The appropriations process, from the President's request through final passage of the bill by the Congress, obligates each Institute to determine how to allocate its own funds among many different activities of science—including investigator-initiated grants, the intramural research program, and research training, among others. These decisions are tailored to the Institute's research objectives.

Each Institute also decides which specific research grant applications to fund among those proposed by researchers working at universities or other research centers and whether to emphasize certain research topics within its domain.

The net effect of these decisions determines how much of the entire NIH budget is devoted to work in certain scientific disciplines (e.g., neurosciences, microbiology, genetics) or on certain diseases.

It is also important to note that past decisions—from the creation of an Institute to the establishment of research centers to the awarding of grants to individual investigators (averaging four years)—have longer lives than the annual appropriations. This leaves only a part of the entire budget available each year for new opportunities.

Assessing research according to money spent on specific diseases is imprecise.

Public and congressional inquiries about how the NIH spends its money often focus on the amounts given to certain Institutes or devoted to research on a specific disease.

- ♦ Research on any disease is not confined to one Institute, and no Institute is dedicated to a single disease. An Institute's budget is an inadequate measure of support for research on specific diseases. Research into many diseases is often carried on in several Institutes simultaneously, e.g., several Institutes are supporting research on Alzheimer's disease.

- ♦ It is also extremely difficult to assign the large investments in basic research to any one disease. For example, the number of grants specifically devoted to heart attacks is smaller than the number of grants awarded for research on cardiac muscle biology and lipid metabolism, which have obvious and promising implications for understanding, preventing, and treating heart attacks.

- ♦ From long experience, we know that research aimed at one target often hits another, e.g., a gene causing breast cancer in mice plays a role in the development of brain tissue. It is impossible to attribute research and discoveries like this to one disease.

There is, consequently, no "right" amount of money, percentage of the budget, or number of projects for any disease.

There are limits to planning science.

Science, dealing with the unknown, is inherently unpredictable (see "How Science Works" later in this booklet). Moreover, unforeseen crises and opportunities may require the NIH and individual scientists to abandon their plans or change the direction and focus of their research. Consider two examples:

- ♦ The emergence of new diseases (AIDS or Ebola), the rise of importance of others as our society changes (Alzheimer's), and the resurgence of old ones (tuberculosis) all require urgent attention. The expense of supporting new and unforeseen research, however, does not displace the need to continue investigations into heart disease, muscular dystrophy, arthritis, or diabetes.

- Unplanned and untargeted basic research on DNA in the 1960s and 1970s permanently changed the way medical research is done. These studies furnished the ground for the biotechnology industry that provides important therapeutic products, which we would otherwise not have, and set the stage for the Human Genome Project that has revolutionized our approach to virtually all disease.

Consequently, slightly over half, on average, of each Institute's budget supports the best research grant proposals regardless of specific applicability to prevention and treatment of a disease, but in expectation that their results will contribute to advances against diseases within their purview as well as diseases in other Institutes and to our knowledge generally.

It is also true, however, that a decision to increase support of one area of medical science—by design, according to a directive, or in response to a critical opportunity—now usually comes at the expense of something else and affects the planning of future research.

Decisions to create new Institutes or to expand research into specific diseases were historically accompanied by very large increases in the NIH budget. No programs had to be cut or attenuated. This is no longer the case. Consequently, directives to spend more on a specific disease or the need to respond to swiftly emerging threats (e.g., Ebola) constrain spending on other diseases or on fundamental research.

Various criteria shape the NIH's budget.

Some general criteria, which condition the allocation of resources, are both influential and continuous.

- The NIH has an obligation to respond to public health needs, as judged by the incidence, severity, and cost of specific disorders. Calculating these needs is difficult, and there is not always a clear correlation between expense and results.

- The NIH applies stringent review for scientific quality on all research proposals in order to return the maximum possible on the public's investment in medical research.

- As an administrator of science, the NIH has learned that many significant advances occur when new findings, often unforeseen, expand experimental possibilities and open new pathways for the imagination. Not all problems are equally approachable, no matter their importance to public health. Pursuit of a rare disease may often have unexpected benefits for more common problems. By the same token, increased spending on a disease is wasteful when there are neither promising pathways to follow nor an adequate number of qualified investigators to fund.

- The NIH's portfolio must be large and diverse. Because we cannot predict discoveries or anticipate the opportunities fresh discoveries will produce, the NIH must support research along a broad—in fact, expanding—frontier.

- The NIH must continue to support the human capital and material assets of science. To this end, the NIH's budget supports research training, acquisition of equipment and instruments, some limited construction projects, and grantee institutions' costs of enabling the research programs.

To develop its research programs, the NIH seeks advice from many sources.

The complexity of both planning budgets and spending money are apparent. With no claim to a monopoly on good ideas, the NIH seeks opinions and counsel from many quarters:

- The extramural scientific community, including both individual researchers and professional societies.

- Patient organizations and voluntary health associations which may deal directly with the NIH or indirectly through Congress and the public media.

- The Congress and the Administration.

- The NIH staff.

How the NIH solicits and acquires opinion and advice is detailed in "The Institutes" and "The Role of the NIH Director," the last two sections of this booklet. Some examples include:

- Review groups of accomplished investigators evaluate grant applications for merit.

- Each Institute convenes national advisory councils to review policy, with members from the public and from the medical and scientific communities.

- Every year, the NIH holds conferences and workshops to gather opinions and ideas on specific scientific, health, ethical, and administrative questions. For example, a Parkinson's workshop recently brought together clinicians and geneticists who together identified a chromosomal locus (and more recently the gene) that predisposes individuals to the familial form of the disease. Their findings will also attract new investigators and could lay the groundwork for advances against the more common (non-familial) form of the disease.

- ♦ The NIH uses advisory groups of outside experts to assess trans-NIH activities (e.g., the reviews of the NIH intramural research program and AIDS research program) and to recommend budgetary and programmatic improvements.

- ♦ In addition to consultations with the Congress, patient organizations, and the Administration, Institute directors and staff seek opinions from other Federal agencies for both budgetary and programmatic insight, e.g., OMB and DHHS.

The final responsibilities for the complex and imperfect process of evaluating opinion, assembling the individual Institutes' portfolios, and determining expenditures remain with the NIH Director and the directors of the Institutes.

Evaluating opportunities and public health needs is complex.

The NIH builds its budget by evaluating current opportunities and public health needs while maintaining strong support for investigator-initiated research. The NIH's requests for increases in funding for specific Institutes are based on proposals that:

- ♦ Exploit new discoveries, such as the isolation of new genes for human disease.

- ♦ Encourage study of diseases that are only now able to be understood because of recent new discoveries.

- ♦ Strengthen technologies applicable to many disciplines and diseases, e.g., computer science, imaging, or gene mapping.

The emphasis the NIH places on funding unsolicited proposals from investigators from individual laboratories (investigator-initiated research) does not dismiss the efforts of advocates of disease-oriented research or propose they should not do more to advance their causes. Nor does the emphasis erect a wall between basic research and clinical research. The Parkinson's disease workshop mentioned above and others on autism, spinal cord injury, and diabetes mellitus have proved how profitable such collaboration can be.

It is also a responsibility of scientists to explain science and scientific progress to the public. Medical science is slow and difficult; its advances do not occur at equal rates on all fronts; the long-term relevance of basic science to treating human disease may be hard to see; scientists may be inexpert in explaining the connection between their work and the nation's health. The many criteria, standards, and influences that all operate simultaneously on the NIH are of themselves complex. There is, however, another component: science is not like other businesses. To explain this proposition, the next section expands on some ideas already here and presents some new ones.

HOW SCIENCE WORKS

Although the word "science" comes from the Latin *scientia* meaning "known things," scientists and the practice of science exist because of what we do not know. The aim of science is to move what we do not know into the realm of known things and then, with a greater store of knowledge, begin again, as if advancing a frontier. This basic truth about science makes it different from other enterprises. Many industries normally manage their resources, labor, and money to produce the same or similar products over and over. Science deploys its resources and talents to explore new areas and produce fresh results, which are not endlessly replicated, but which prepare the way for future and different explorations.

The many disciplines of medical research contribute to our store of knowledge and to one another, and all deserve exploration and funding. Discoveries that will increase our knowledge of the causes, progression, and treatment of asthma, for example, may stem from epidemiological, clinical, and molecular research, conducted by teams of investigators building on the discoveries of their predecessors, including those in other fields.

Since it is impossible to know with certainty which area will produce the next important discovery, the community of science, of which the NIH is a part, has to be open to all ideas. No one field has all the answers, but investigators in many different fields can ask the questions that will provide more knowledge about disease and health.

The uncertainty of where the most valuable discovery lies makes the setting of priorities tremendously difficult. But this uncertainty also fosters a creative and collaborative tension within the scientific community (and among the various Institutes at the NIH) which in turn imposes the discipline of evaluation, competition, and productivity on the choices we make about spending public money.

To approach it differently, science and the management of science are neither chaotic nor navigation by dead reckoning. Given the NIH's internal rigor and the legitimate interests of the public, including advocacy and patient groups, the Congress, and other scientists, expenditures for medical research are always in public view. Though different from other enterprises, science has businesslike aspects: Applications for grants are subject to peer review (which is discussed later in this booklet) and rated for merit, and investigators define and justify the goals and budgets of their research with precision.

It is a striking characteristic of science that it requires both creativity and precision to generate ideas and results. The precision with which investigators and administrators describe the targets and outcomes of research, however, cannot alter the inescapable truth that many of the results of research are unpredictable, given the pursuit of unknown things. The investigator examining patients with ataxia telangiectasia, a rare genetic disease, who discovers something new about the origins of cancer has not "stumbled" on a discovery, but rather has put himself or herself in a position to make the discovery and to bring it into the realm of known things which would not have happened otherwise.

This unpredictability has three important implications of its own.

First, science is by nature structured and self-correcting so that either a predicted or an unforeseen discovery has the advantage of adding to basic scientific knowledge and giving new direction to further inquiries. This self-correction, carried out under public scrutiny of the results, means that science operates in a dynamic marketplace in which an absolute or top-down control would be stifling. Control from the top or by directive grows inefficient as workers duplicate one another's labor or merely produce the same results; it tends to be slow to respond to new discoveries which can make the original grand design obsolete overnight. Science's self-correction, on the contrary, demands more approaches and is quicker to adapt to change.

Second, scientific work is not a commodity that can simply be bought. Shifting priorities is more than the redistribution of dollars–more money alone does not solve problems. Recruiting new talent by advertising a new scientific opportunity, inviting scientists in allied fields to look across the fence, and training new investigators to work in a new area will produce more meritorious applications for funding and, most important, better results in the treatment of human disease.

Third, science and its administrators must constantly reevaluate and often change their priorities in light of new discoveries. Very simply, science itself sets its priorities as it refreshes and enlarges our knowledge: The more we know, the better the questions we can ask and the more wisely we can spend our money.

It is by asking as many questions as we can and by prudently spending what we have that the NIH can identify and pursue the most promising medical priorities. As priorities shift and acquire sharper focus, we are better able to look across the spectrum of scientific disciplines and of diseases. Our constantly renewed knowledge enables us to examine, for example, the effects of pesticides not on one kind of cancer but on all cancers, or to ask the next big question–what turns genes on or off?—with the confidence that we will soon begin to find answers which in turn will allow us to target diseases like Alzheimer's disease, cancer, and diabetes.

There are many reasons that America is blessed with a robust community of medical science and that the NIH is the world's greatest medical research organization. The freedom to explore, the training in our colleges and universities, an enthusiastic public, and an understanding Congress have all contributed to the nation's preeminence in medical research. And so, in part, has the community of science itself because of its abilities to refresh its priorities in order to seek opportunities that are ripe for pursuit and capture.

The rest of this booklet describes the principles and processes by which the NIH and its Institutes set their priorities and make their choices. It will also consider in greater detail the roles played by the Congress and the Administration, by professional societies, and by organizations focused on particular diseases in funding the research that brings what we do not know into the realm of known things.

THE NIH'S HISTORY

Decisions made in the NIH's early years still shape the agency's structure and activities. The NIH as we know it today is rooted in Constitutional language establishing the promotion of the general welfare as a goal of government. Throughout this country's history, citizens have looked to government to provide health care to specific populations, for collection of vital statistics on health, and for sanitation and control of infectious diseases. Although the NIH was born on Staten Island in 1887, with another name and a mission to conduct research on infectious diseases, the modern NIH took shape shortly after World War II, when science came to be seen as a public good and supporting health research became a focus for public and congressional enthusiasm and funding.

In 1946, the NIH intramural research program (the research conducted by government scientists on the NIH campus in Bethesda, Maryland, since 1938) was joined by the NIH extramural research program. This occurred when wartime government medical research contracts at universities and medical schools around the country were transferred to the NIH and converted into grants. The transfer was an important event, for it firmly established the importance of enlisting scientists in the country's medical schools and universities in the national research effort against disease.

Just after the extramural research program began providing grants to scientists in universities and medical schools, the NIH recognized it needed a system to help select the highest quality

research grant applications for funding. This rapidly evolved into the NIH peer review system, which relies chiefly on non-government scientists to review grant applications for scientific merit.

The NIH also recognized that supporting research demands a greater commitment than simply funding individual research projects. Since 1947, NIH grants have included compensation to the institutions where the research is to be conducted for the expenses of maintaining the research facilities and for administering the grants. Training future generations of laboratory and clinical researchers also became an established goal of federal funding of science.

The intramural research program on the Bethesda campus—which primarily focused on basic or laboratory science—was enhanced by the opening of its research hospital, the Clinical Center, in 1953. This addition acknowledged the importance of translating discoveries made in the laboratories to the bedside, and provided a way of taking questions raised through observation of patients back to the laboratory for exploration. The need to fund both laboratory research and clinical research thus became an established principle.

Encouraged by the availability of public funding, growing numbers of investigators around the country—many of them trained on the Bethesda campus—directed their efforts to basic and clinical research and applied to the NIH for research grants. The NIH cultivated the cadre of talented, well-trained scientists eager to propose their ideas to the NIH for funding, thus creating the investigator-initiated research application as a way of tapping the best ideas to understand and combat disease.

The following two decades saw significant increases in funding for the NIH and the development of new programs. New Institutes continued to appear in response to legislative or executive decisions. The establishment of each new Institute represented a decision about the priority to be given to a disease or class of diseases (for example, the National Institute of Allergy and Infectious Diseases was established in 1948 and the National Institute of Neurological Diseases and Blindness in 1950), to aspects of the human life span (the National Institute of Child Health and Human Development was established in 1963 and the National Institute on Aging in 1974), and to broad areas of basic research and technology (the National Institute of General Medical Sciences was established in 1963 and the National Library of Medicine became a component of the NIH in 1968). Each of the NIH Institutes has been provided a separate, annual budget from the Congress, thus positioning each of them as a primary locus for setting priorities and making budget decisions within their domains. (See Appendix for list of Institutes)

HOW THE NIH FUNDS MEDICAL RESEARCH

Most of the NIH's budget supports the individual research projects conceived of and conducted by either government scientists working on the NIH campus or scientists based elsewhere, at universities, medical, dental, nursing, and pharmacy schools, schools of public health, non-profit research foundations, and private research laboratories. These scientists have been trained in one or more disciplines of science and are committed to enhancing knowledge related to human health and disease through research. NIH support of these research projects includes the salaries of scientists and technicians and the cost of equipment such as lasers or computers; of supplies such as chemicals and test tubes; and of procedures conducted with research patients.

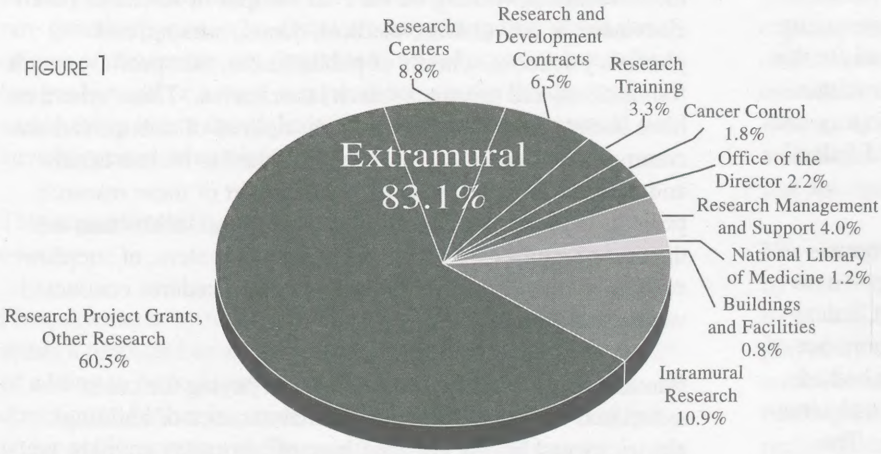
Funding medical research also includes paying the costs associated with research, such as maintenance of buildings, electricity and library services, care of laboratory animals, and salaries of administrative staff who, for example, handle the financial aspects of the grants and set up review panels to ensure that patients participating in research are adequately protected. This is true for all research, whether conducted in the intramural program by government scientists or through the extramural program by scientists in universities and medical schools or by scientists working in industry. These associated costs account for about 30 percent of the total cost of research projects.

In fiscal year 1996, approximately 11 percent of the NIH budget was spent in the intramural program and more than 83 percent of the NIH budget was used to fund research by scientists working elsewhere across the country (SEE FIGURE 1). In the extramural program, the NIH emphasizes funding investigator-initiated applications that originate with individual scientists. These Research Project Grants (or RPGs) can fall anywhere along the continuum of medical research, from molecular and cellular investigations to studies of new drugs to treat human illness. In Fiscal Year 1996, the NIH funded approximately 25,000 RPGs; the most common type, known as an R01 grant, supports a single project and a single principal scientist. Some Research Project Grants are program project grants, which support multi-disciplinary projects conducted by several investigators working on different aspects of a research problem. Yet another way the NIH supports research is through research centers. This type of grant is awarded to research institutions under the leadership of a center director and a group of collaborating investigators. Center grants fund multi-disciplinary programs of medical research and also support the development of research resources, aimed at integrating basic research with applied research and promoting research on clinical applications.

National Institutes of Health FY 1996 Budget *

$11.9 Billion

FIGURE 1



* FY 1996 is the most recent year for which dollar distribution is available.

Another part of the NIH's budget is spent on research and development contracts, which are awarded to non-profit and commercial organizations for work requested and overseen by the NIH staff. For example, development of the drug taxol for treating breast and ovarian cancer resulted from NIH contracts aimed at developing better methods for isolating the anti-cancer agent from the Pacific yew tree and for clinical trials of its efficacy.

The NIH also supports training that enables young scientists to become skilled investigators who are available to apply their talents to future medical challenges. Trainees, who are at the predoctoral or postdoctoral level, are supported through grants either to individuals or to institutions such as medical schools and universities. Most of the cost is for stipends for the students. In recent years, the NIH has focused on enhancing the quality of training and improving the prospects for under-represented minorities rather than on increasing the total number of students in research training.

An imperative of supporting medical research is making a commitment to scientists to fund their work for a period of time sufficient for the projects to produce results. Research takes time. NIH grants are awarded for an average of four years; therefore, the bulk of each Institute's annual budget is already committed to funding the remaining years of research projects. The need to continue funding projects over multiple years is an important criterion when deciding to fund new projects. Accordingly, in any given year, only about 25 percent of the total funds allocated for research projects is available to fund new projects that may change the course of a line of research or move research into an entirely new area.

ASSESSING HEALTH NEEDS AND SCIENTIFIC OPPORTUNITIES

Deciding how and where to distribute the NIH's money—that is, determining the requirements of basic and clinical research, identifying whether a grant, contract, or center is the best means of funding a particular area of research, and responding to the emergence of new medical problems and new patient advocacies—is a challenge the NIH must face each year. It requires fresh assessment of the nation's health needs and renewed evaluation of scientific opportunity. Yet there are many ways of assessing health needs and many facets to identifying, and sometimes creating, scientific opportunities.

Assessing the health needs of the nation.

The NIH is responsible for conducting research on the broad array of health problems affecting people in this country, but it cannot simply allocate funds to research on one disease or another according to a set formula. There are many possible ways of measuring the health needs of the nation and distributing research funds, each with advantages and drawbacks. If health needs alone were used to gauge priorities, research funds might be distributed based on:

- ♦ The number of people who have a particular disease.
- ♦ The number of deaths caused by a disease.
- ♦ The degree of disability produced by a disease.
- ♦ The degree to which a disease cuts short a normal, productive, comfortable lifetime.
- ♦ The economic and social costs of a disease.
- ♦ The need to act rapidly to control the spread of a disease.

Using any one of these criteria to make funding decisions would produce a different result:

- Funding according to the number of individuals affected would emphasize common diseases, but might have a limited effect on overall health and survival (for example, much research would be done on the common cold and allergies and little on childhood cancers).
- Funding according to the number of deaths would neglect chronic diseases that produce long-term disability and high costs to society (diseases such as mental illness and arthritis would be neglected).
- Funding according to disability or economic cost raises questions about how well disability or economic costs can be quantified, and whether only the direct costs of medical care should be counted or whether indirect costs (e.g., lost productivity), which are difficult to measure, should also be included.
- Funding according to the economic cost of illness would under-fund diseases that result in a short illness and rapid death (this choice would provide a great deal of funding for Alzheimer's disease and muscular dystrophy and little, or none, for sudden infant death syndrome or certain types of cancer).
- Funding based solely on immediate dangers to public health may divert funds from areas of research of much broader long-term impact (this choice would mean that a great deal of research would be done on AIDS and tuberculosis and little on Parkinson's disease and asthma).

All of these criteria for weighing health needs are justifiable, yet applying any one of them exclusively would cause the neglect of some classes of diseases altogether. Moreover, any of these criteria used exclusively would, for example, under-fund research on rare diseases, research that has taught us much about the diseases themselves and a great deal about normal human biology, other diseases, and new approaches to treatment. For example, ataxia telangiectasia, xeroderma pigmentosum, and Bloom's syndrome are very rare inherited disorders that lead to an increased risk of cancer and hypersensitivity to ultraviolet radiation, X-rays, and some chemicals that cause mutations in DNA. Nonetheless, research into these diseases has not only helped people with those conditions, but has provided considerable knowledge about the causes of cancer in general.

Funding the continuum of research, from basic inquiries to clinical applications.

Clearly, it is not easy to determine how to allocate funds according to the impact of various diseases. But the problem is actually much more complex than it appears, because while the NIH focuses much of its research on combating specific diseases and much of its funding supports research projects that are of obvious relevance to specific diseases, the NIH also places a high priority on funding basic research. These basic research projects may appear initially to be unrelated to any specific disease, but might prove to be a critical turning point in a long chain of discoveries leading to improved health. Each of the NIH Institutes supports basic research likely to advance particular areas of science that might prove relevant to clinical problems important to that Institute's mission. By supporting disease-related and basic research projects simultaneously, the NIH can achieve both near-term improvements in the diagnosis, treatment, and prevention of specific diseases as well as long-term discoveries in basic science that in time will produce great advances in our ability to understand, treat, and prevent disease or delay its onset.

The unexpected contribution of basic research to specific diseases is evident in the case of recombinant DNA research, sometimes called genetic engineering. NIH support of basic research on enzymes and genes over many decades, exciting and challenging to scientists but initially with no apparent relevance to practical applications or human disease, has led to a host of new drugs and diagnostics. For example, in the mid-1980s human growth hormone produced by recombinant DNA methods was approved for treating certain growth problems in children. This synthetic human growth hormone proved to be safer than using pituitary-derived human growth hormone extracted from cadavers, which had been found to transmit the virus causing Jakob-Creutzfeldt disease, a deadly neurological disorder. In addition, recombinant DNA techniques revolutionized how biological research is done and gave rise to a new industry—biotechnology. This technology, in just over a decade, has had a profound impact upon medicine, agriculture, and the chemical industry.

Consequently, the NIH uses no one measure exclusively, but all of these measures to assess the nation's health needs. The evidence of improved health in the past 50 years overwhelmingly demonstrates the importance of complementary accomplishments in basic and applied research. To continue improving the nation's health, the NIH also factors into its funding decisions current and evolving scientific opportunities.

Assessing scientific opportunities.

Assessing scientific opportunities is no less complex than evaluating health needs. It requires expertise in various scientific fields, breadth of vision across many disciplines, and judgment to determine the likely yield from making investments in particular areas of research. It is never known with certainty which scientific areas will produce the greatest returns soonest. At any given time, moreover, some fields are judged to be progressing more rapidly than others and more likely to repay the investment in them by yielding great discoveries that advance knowledge. Scientific opportunities may arise from many sources, from a single technological development, or from a scientific "breakthrough." Often the breakthrough or even the knowledge accumulated is in an area that appears only remotely related to the area where it will have its greatest impact. Recognition of these scientific opportunities allow investigators to approach previously unanswered questions in new ways.

Work in blood lipid research and heart disease illustrates how health needs and scientific opportunities coincide. Nearly 50 years ago, the NIH identified research on coronary heart disease as an important health priority. This disease is caused by atherosclerosis, the build up of lipids (fatty substances) in the heart's main arteries, which can block blood flow and thereby cause the death of heart tissue—that is to say, a heart attack. Progress in this area was slow at first, but then scientists began to associate lipids (such as cholesterol, carried in the blood) with the development of atherosclerosis in humans. In the early 1960s, research on the NIH Bethesda campus led to a way of classifying various types of lipid abnormalities in families. This work led to meaningful associations between variations in lipid metabolism and atherosclerotic heart disease. In addition, through carefully planned, long-term epidemiologic studies (studies of the occurrence and distribution of disease in large groups of people), the understanding emerged that risk factors such as blood cholesterol levels and cigarette smoking, as well as high blood pressure (which was recognized much earlier as a predictor of premature death) can make people susceptible to disease. Identifying scientific opportunities in basic, clinical, and epidemiological research on lipid metabolism has resulted in phenomenal progress in understanding the underlying processes that lead to atherosclerosis, as well as its prevention and treatment.

Benefits from this research include the development of cholesterol-lowering drugs and changes in behavior (less dietary fat, no smoking, more exercise), with a dramatic decrease in age-adjusted mortality from heart disease as a consequence. Still, many challenges in coronary heart disease remain. Future targeted areas of research include an analysis of why cholesterol accumulates in artery walls and ways to facilitate its removal, and prevention of the accelerated

As an example of a breakthrough offering new opportunities, consider recent discoveries in the causes of obesity, which have stimulated the NIH to invest more money in this particular area of research. Obesity affects nearly one-third of the U.S. population. It is associated with an increased risk of high blood pressure, high blood cholesterol, and Type II diabetes (or non-insulin dependent diabetes) and is an independent risk factor for coronary heart disease and osteoarthritis. Obesity has been studied for many years from many perspectives, and is of interest to at least 10 NIH Institutes. But the problem has remained intractable. Recently, scientists have found that mice and rats with certain inherited mutations that predispose to obesity lack a hormonal mechanism for maintaining healthy patterns of eating and activity. Through this mechanism, the animals—and, presumably, humans—regulate diet and exercise through the brain's response to a hormone, called leptin, that is produced by fat cells. Although it appears likely that this hormone is itself deficient in a significant number of obese people, the isolation of the genes for leptin and the leptin receptor has already deepened our understanding of metabolism and stimulated additional fundamental research. Encouraged by the new findings, more and more scientists are moving into this field of investigation. This is likely to expand knowledge of the causes of obesity, hasten the development of more effective medical therapies for weight problems, and ultimately help to reduce the prevalence of many chronic, obesity-related diseases.

form of atherosclerosis which causes between 30 and 40 percent of grafts to become narrowed again after bypass surgery.

Capitalizing on scientific opportunity depends, in part, on individual scientists designing specific research projects they believe have the greatest significance and offer the best chance of producing important knowledge. Therefore, the NIH places great reliance on investigator-initiated research—projects conceived by individual scientists and submitted to the NIH to undergo review by other scientists and be considered for funding. Sometimes, the NIH solicits research applications through Program Announcements (PAs) and Requests for Applications (RFAs), as described in more detail later in the booklet. Review for scientific merit is conducted by groups of predominantly non-government scientists (with knowledge in a relevant area) convened as panels called study sections. Currently, there are about 100 study sections, which normally meet three times a year to review grant applications.

The merit of a research proposal is assessed by several criteria, including: the importance of the problem or question; the innovation employed in approaching the problem; the adequacy of the methodology proposed; the qualifications and experience of the investigator; and the scientific environment in which the work will be done. Currently, slightly more than one in four grant applications received by the NIH is ultimately funded. (SEE FIGURE 2)

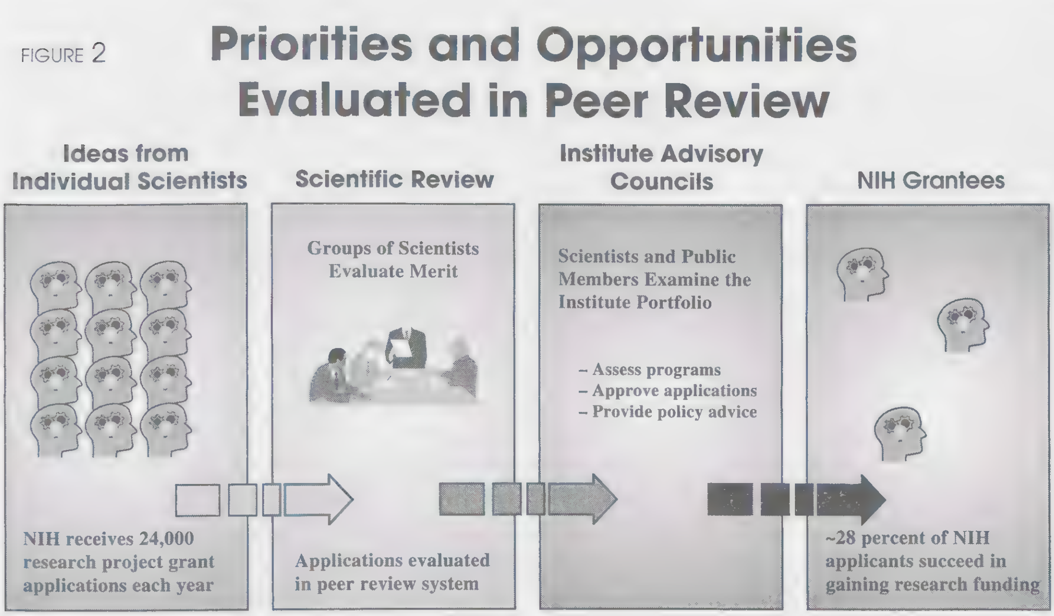
In addition to judging the scientific merit of individual research grant applications, the study sections, in aggregate, have another important effect on the science supported by the NIH. After each study section reviews and rates the grant applications assigned to it by NIH staff, the relative ratings of applications from all study sections are then integrated. Because, for the most part, grants are funded in order of their rating relative to other applications in the same field, the fact that a study section has been constituted in a particular area usually guarantees that at least some applications in that area of science will be funded. Because of this effect, the NIH must monitor changes occurring in science to ensure that study sections, as a group, are appropriately constituted so that they can assess the research applications in all areas of scientific endeavor. The creation of new study sections, the restructuring of established study sections, and the use of special panels has such an important effect upon the areas of science funded by the NIH that any proposed changes of the study sections are carefully evaluated.

THE INSTITUTES

The NIH is made up of 21 Institutes and Centers, each with a separate, annual budget from the Congress and, most critical to the question of priorities, each with a mission established by the Congress. To decide which grants to fund and which programs to support in terms of its mission, the director of each Institute confers with the Institute's program leaders. Like the director, they are scientists knowledgeable in research relevant to the Institute's mission and responsible for administering that area of research. The director also confers with members of the Institute's national advisory council (as mandated by the Congress), which meets three or four times a year to review all grant applications eligible for funding (after peer review) and to make recommendations on matters of policy and research emphasis. The council, which is composed of both scientific and public members with expertise relevant to the Institute's mission, may also make recommendations to the Institute director about funding particular, meritorious grants that are seen as very important but which may not have received the best scores from scientific reviewers. The council may also review and comment on special initiatives proposed by the Institute or, for example, on research training policies.

The director engages in discussions with scientists in the extramural program and intramural investigators, with groups of patients and their families interested in research on particu-

FIGURE 2



lar diseases, with professional and scientific groups, with representatives of the Administration and members of Congress, and with the public. (SEE FIGURE 3)

Advice is sought on many issues, including:

- The potential impact of particular research areas on human health.
- The critical scientific opportunities.
- Gaps in knowledge that merit special effort.
- The cost of specific research projects and their benefits.
- Economic issues, including the potential effects of the research on quality of life.
- The balance between intramural and extramural research.
- The balance among laboratory research, clinical research, and epidemiological research.
- The specific type of funding to use for various research areas, for example, selecting among grants, contracts, and support of centers (see definitions of the types of funding on pages 7-8).

Funding the highest quality science.

The advice an Institute director receives from many sources on the factors enumerated above provides much of the information needed to decide which grants and programs to support and which programs to initiate or eliminate.

As described on pages 7-8, research projects emerge from the creativity, skill, and knowledge of extramural scientists who submit grant applications to the NIH. These are reviewed by panels of scientists who are expert in the proposed field of research. Intramural scientists are also peer reviewed by special groups called Boards of Scientific Counselors, consisting of scientific experts chosen mainly from outside the government (see page 14). Thus, it is the highest rated projects that form the backbone of the science funded by the Institutes and by the NIH. The outstanding ideas of scientists objectively rated for their own merit and against publicly stated criteria, like those listed in the previous section, guide the funding decisions of the NIH.

Creating research opportunities.

While over half of the Institutes' funds support grant applications submitted by scientists working in universities, medical schools, other professional schools, and independent research

An example of a cross-Institute collaboration that has produced a distinct benefit is the collaboration between the National Institute of Neurological Disorders and Stroke (NINDS) and the National Human Genome Research Institute (NHGRI) in Parkinson's disease. Parkinson's disease is one of the most devastating and prevalent neurodegenerative disorders. The advent of dopamine replacement therapy in the 1960s provided significant improvement for many patients, but the effectiveness of the treatment declines over time and there are troublesome side effects. There has been great interest among both patients and researchers to develop a more effective treatment or even to prevent the disease, but the mechanism of Parkinson's disease is not sufficiently understood. In 1995, a group of scientists called together by NINDS and other Institutes concerned with Parkinson's disease reached the unexpected conclusion that Parkinson's disease is likely to have a stronger genetic component than was previously thought. NINDS subsequently issued a Program Announcement inviting research grant applications in the genetics of Parkinson's. In addition, a collaboration involving NHGRI intramural scientists and NINDS grantees was established to study the genetics of families affected by Parkinson's. In November 1996, scientists from the NHGRI and NINDS and their collaborators at Robert Wood Johnson Medical School and in Italy announced they had pinpointed the location of a gene responsible for some cases of Parkinson's disease, showing that a single gene alteration can cause the disease. In June 1997, the specific responsible gene was identified. Learning where the protein product of the gene is located in nerve cells and how it works may help scientists design treatments for all forms of Parkinson's disease—not only inherited cases, but also those with no familial risk.

centers on subjects they deem important, there is also a complementary process within the Institutes to look at broad areas of science and identify areas of research where special emphasis is warranted. The scientific program leaders in the Institutes help identify scientific opportunities or techniques ripe for application by staying abreast of the scientific literature and attending conferences and meetings of professional societies where new basic and clinical findings are presented and debated. If, for example, an Institute is convinced that a particular area of science offers opportunity, but extramural scientists are not generating research proposals in that area, the Institute may decide to organize a workshop or conference to identify specific scientific needs and opportunities, stimulate research applications, and attract scientists into the field. Or if an Institute wants to encourage extramural scientists to apply their particular skills to a new challenge, Institute program leaders may generate a concept that will become a Program Announcement (PA), an ongoing request for applications in a broad area of interest, or a Request for Applications (RFA), a one-time request for applications addressing a specific scientific area. While only a small percentage of an Institute's funds is spent on research generated in response to RFAs and PAs, this modest investment has been a catalyst for scientific progress.

Although funding is usually determined by the scientific merit of research applications, an Institute may determine that an area of research is of such great promise that funding is provided even if the grant application does not have as high a relative rating as other applications. Only the Institute director has the authority to make this decision and it requires his or her awareness of the whole picture of the Institute's mission. The Institute director may determine that some laboratory research areas are in need of greater attention and require more funding or that some areas are ripe for translating laboratory or animal studies to patients in clinical research studies. The Institute director would discuss these decisions with council members (and others) before funding this research.

The Institutes may also collaborate on common research interests or to advance certain topics of research. For example, both the National Institute of Neurological Disorders and Stroke and the National Heart, Lung, and Blood Institute are interested in stroke, and five Institutes—the National Institute of Arthritis, and Musculoskeletal and Skin Diseases, the National Institute on Aging, the National Institute of Dental Research, the National Institute of Diabetes, Digestive and Kidney Diseases, and the National Institute of Child Health and Human Development—are interested in osteoporosis. Each Institute brings a different perspective and interest to an issue, so their collaborations encourage a multi-disciplinary approach to research problems. Sometimes, Institutes co-fund research projects that are important to the mission of each.

The Institutes sometimes also co-fund research programs with agencies outside the NIH when a scientific opportunity is ripe for both agencies. For example, the National Cancer Institute has collaborated with the Department of Defense on breast cancer studies, and the National Heart, Lung, and Blood Institute has worked with the Health Care Financing Administration on clinical trials of lung reduction surgery in the late stages of emphysema.

The Intramural Research Program.

Most of the Institutes have intramural research programs.

Two particular characteristics of the NIH intramural research program proved advantageous at the start of the AIDS epidemic, even before the disease was named. First, the intramural program has the flexibility to redirect resources and expertise quickly when an urgent research problem or public health threat is recognized. In addition, the intramural program has a concentrated expertise focused exclusively on research, and an atmosphere that encourages discussions and collaborations across disciplines. Intramural scientists studying the immune system and virologists studying the cause of AIDS were able to draw on colleagues in, for example, the dental, neurological, and eye Institutes for consultations on particular clinical manifestations of AIDS. An informal series of patient conferences was set up at the very beginning of the epidemic, in the early 1980s. This concentrated effort led to major accomplishments in AIDS research by the NIH intramural program, for example: a detailed description of the effects of HIV on the immune system; development of a treatment for a viral infection, cytomegalovirus, causing blindness in AIDS patients; early development of policies to screen blood donors (and hence to prevent the further spread of AIDS through the blood supply); understanding of the unusual proteins encoded by HIV genes; development of a blood test for HIV; formulation of hospital guidelines for working safely with AIDS patients; and early studies of the first treatment for AIDS, the drug AZT.

Amounting to approximately 11 percent of the total NIH budget in fiscal year 1996, they focus on specific health problems of special concern to a particular Institute and conduct basic research that may not target a specific disease, but relates to the overall mission of the Institute. As with extramural research, program adjustments, driven by scientific opportunity, are constantly being made to the intramural research programs. The Institute intramural research programs are led by scientific directors, outstanding scientists who, with the Institute director, are responsible for organizing and administering both laboratory and clinical research. They undergo peer review by a Board of Scientific Counselors, which advises the director of the Institute on the importance and quality of the programs, thus providing yet further scrutiny of the distribution of resources to particular research areas and scientists. The intramural programs of the Institutes are also reviewed by the national advisory councils and, sometimes, by additional panels of outside experts convened to address specific issues.

Ideas from outside the NIH also influence research choices. For example, in 1971 President Nixon signed the National Cancer Act, making cancer research a national priority. The Congress, responding to constituents, has also influenced NIH priorities by occasionally identifying research areas that the Institutes should consider more intensely. The Institute directors meet with congressional members and staff throughout the year, and formally during the annual budget hearings, to discuss the research advances of each Institute during the past year and describe their plans for the next. Through both the Administration and Congress, as well as through patient advocacy groups, the public influences the Institutes' decisions. In addition, the national advisory councils set up by each Institute and other NIH advisory committees include members specifically designated as "public" representatives. Proposals and opinions from scientists, the Congress, the Administration, and the public assure that the Institutes establish their priorities in the light of many views. Ultimate responsibility for the allocation of financial and other resources of an Institute rests with the Institute director. After careful evaluation of all of the factors described above, the Institute director determines how and where the Institute's resources will be distributed.

THE ROLE OF THE NIH DIRECTOR

Though each Institute within the NIH determines how it will deploy its talent and funds, the NIH Director plays an active role in shaping the agency's activities and outlook. With a unique and critical perspective on the whole of the NIH, the Director is responsible for providing leadership to the Institutes and for constantly identifying needs and opportunities, especially for efforts that involve multiple Institutes. The Director stays in touch with each Institute's priorities and accomplishments through regular senior staff meetings, discussions with scientific interest groups (scientists who have interests in a

FIGURE 3

Setting Research Priorities: Every Voice Counts

specific area and can provide guidance in solving scientific questions), and briefing sessions with Institute directors. The Director also seeks advice from special panels of experts convened to address issues that are of interest to more than one Institute, e.g., reviews of NIH support of research relevant to human gene therapy, the NIH investment in clinical research, the operation of the NIH intramural research program, and the effectiveness of the NIH peer review procedures. In addition to this flow of information from scientists, the Director is advised through discussions with the Administration, usually through the Department of Health and Human Services (DHHS), and with the Congress.

Within the NIH, the NIH Director is primarily responsible for advising the President on his annual budget request to Congress on the basis of extensive discussions with the Institute Directors. The formulation and presentation of the NIH budget provides an established framework within which priorities are identified, reviewed, and justified. A key strategy of the NIH Director in the past few years is the identification of Areas of Research Emphasis, broad categories of NIH-sponsored research that show extraordinary promise and productivity. Each year, the NIH Director requests proposals from the Institutes for areas of research that would benefit from special emphasis. Six broad areas of emphasis have been identified for fiscal year 1998; five of these, including "Biology of Brain Disorders," "New Approaches to Pathogenesis," "New Preventive Strategies Against Disease," "Genetic Medicine," and "Advanced Instrumentation and Computers," were also identified in fiscal year 1997. A new Area of Research Emphasis, "New Avenues for Development of Therapeutics," emerged from consideration of Institute proposals for new initiatives for fiscal year 1998. The Institutes are encouraged to develop new initiatives within these Areas of Research Emphasis and to respond to emerging health needs through both inter- and intra-Institute efforts. The NIH Director uses these proposals to build the President's budget in order to ensure that new initiatives are meritorious and timely and that budget increases are used to capitalize on recent scientific developments.
The Director has two additional tools to identify and fund NIH research efforts. First, the Director may, following a clearly defined process, transfer up to one percent of the total NIH budget among Institutes. Second, the Director has a Discretionary Fund. Both are used to jump-start particularly exciting or urgent areas of research:

- Transfer funding from the Director typically follows extensive discussions between and among the NIH Director and the Institute directors, and advice from outside experts to identify particular research initiatives that reflect NIH-wide priorities, show real promise, or reflect an emerging need that requires a timely infusion of funds. DHHS, the Administration, and congressional appropriations subcommittees are then notified of the NIH intent to transfer the money. No single Institute can lose more than one percent of its appropriated funds in this process.

- The NIH Director uses the Discretionary Fund, as appropriated for this purpose by the Congress, to support specific research opportunities that arise during the course of a year that would otherwise have to wait until the following year for funding. The NIH Director can, in this way, provide early support to research by giving additional funds to a single Institute or to several Institutes. The NIH Director can also use these funds to respond to specific requests from the Congress or to a public health emergency. One way the Director's Discretionary Fund has been used in recent years is to fund the Shannon Awards (named after an illustrious former NIH Director), which provide some funding for deserving projects that could not be paid for within the available budget. This is a means of keeping investigators, especially new investigators, active scientifically until funding becomes available for supporting their research applications.

Program offices in the Office of the Director are also responsible for enhancing some of the cross-Institute coordination of, for example, minority health, disease prevention, rare diseases, behavioral and social science research, and complementary and alternative medicine. Another program office is the Office of AIDS Research, which has been given broad legislative authority to plan, coordinate, evaluate and budget all NIH AIDS research. The NIH is strongly committed to identifying, developing, and pursuing research that reflects broad approaches to understanding human illness and health.

Many diseases under study at the NIH require the input of more than one Institute. While the Institutes themselves enjoy close collegial relationships and employ a number of mechanisms to foster their collaborations, the NIH Director has a unique overview of the range of endeavors across the entire NIH. The Director thus can influence all the Institutes to focus on matters of importance to them all.

CONCLUSION

All of the activities described here have the common purpose of informing the NIH of scientific opportunities and of important needs in public health. Recognizing needs — and establishing priorities among them— stimulates the most promising medical research and advances our knowledge. The continuing dialogue between the public and scientists ensures a system that is both stable and responsive—a system that effectively and efficiently meets its goal to improve the nation's health through medical research.

NIH's Institutes and Centers*

Dates Established

National Cancer Institute (NCI) - 1937

National Eye Institute (NEI) - 1968

National Heart, Lung, and Blood Institute (NHLBI) - 1948

National Human Genome Research Institute (NHGRI) - 1989

National Institute on Aging (NIA) - 1974

National Institute on Alcohol Abuse and Alcoholism (NIAAA) - 1970

National Institute of Allergy and Infectious Diseases (NIAID) - 1948

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) - 1986

National Institute of Child Health and Human Development (NICHD) - 1963

National Institute on Deafness and Other Communication Disorders (NIDCD) - 1988

National Institute of Dental Research (NIDR) - 1948

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) - 1950

National Institute on Drug Abuse (NIDA) - 1974

National Institute of Environmental Health Sciences (NIEHS) - 1966

National Institute of General Medical Sciences (NIGMS) - 1963

National Institute of Mental Health (NIMH) - 1946

National Institute of Neurological Disorders and Stroke (NINDS) - 1950

National Institute of Nursing Research (NINR) - 1986

National Library of Medicine (NLM) - 1968, became a part of the NIH

National Center for Research Resources (NCRR) - 1956

John E. Fogarty International Center (FIC) - 1968

*Each with a separate annual budget from the Congress.

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National Institute of Nursing Research [illegible]

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[illegible] for Research Resources [illegible] - 1962

[illegible] International Center [illegible]

*Each with a separate annual budget from the Congress.

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